SYNOPSIS

Title of the study: A randomized, double-blind, placebo-controlled, parallel-group, multicenter, 24-week study followed by an extension assessing the efficacy and safety of AVE0010 in 2 titration regimens on top of metformin in patients with type 2 diabetes not adequately controlled with metformin (EFC10743)

Investigator(s): [redacted]

Study center(s): Multicenter (75 centers in 15 countries)

Publications (reference): Not applicable.

Study period:

Date first patient enrolled: 29-Sep-2008

Date last patient completed: 27-Jan-2011

Phase of development: 3

Objectives:

Primary: To assess the effects of AVE0010 (hereinafter referred to by the international nonproprietary name, lixisenatide) as an add-on treatment to metformin on glycemic control using a 2-step dose titration regimen in comparison to placebo in terms of glycosylated hemoglobin (HbA_{1c}) reduction (absolute change) over a period of 24 weeks in patients with type 2 diabetes.

Secondary:

To assess the effects of lixisenatide on:

- Glycemic control in comparison to placebo in terms of HbA_{1c} reduction when it is used in a 1-step dose titration regimen,
- Percentage of patients reaching HbA_{1c} <7% or HbA_{1c} ≤6.5%,
- Body weight,
- Fasting plasma glucose (FPG);

To assess lixisenatide safety and tolerability;
To access lixisenatide pharmacokinetics (PK) and anti-lixisenatide antibody development.

Methodology: This was a randomized, double-blind, placebo-controlled, 4-arm, unbalanced design, parallel-group study with a 2-step titration regimen (10 µg once daily [QD] for 1 week, then 15 µg QD for 1 week, followed by the maintenance dose of 20 µg QD) or a 1-step titration regimen (10 µg for 2 weeks followed by the maintenance dose of 20 µg QD). The study was double-blind with regard to active and placebo treatments; however neither the study drug volume nor the titration regimens (ie, 2-step or 1-step) were blinded.

Number of patients:	Planned:	450	Randomized:	484	Treated:	482
Evaluated:	Efficacy:	479	Safety:	482	Pharmacokinetics:	475

Diagnosis and criteria for inclusion: Patients with type 2 diabetes mellitus (T2DM) diagnosed at least 1 year before the screening visit; insufficiently controlled with metformin at a stable dose of at least 1.5 g/day for at least 3 months prior to screening; and HbA_{1c} ≥7.0% and ≤10% at screening.

Investigational product: lixisenatide

Dose: 10 µg, 15 µg, and 20 µg

Administration: subcutaneous injection

Batch number(s): [redacted]

Duration of treatment: At least 76 weeks (24 weeks main double-blind treatment; variable double-blind extension)

Duration of observation: Approximate minimum duration of 79 weeks (up to 2 weeks screening + 1 week run-in + 24 weeks main double-blind treatment + variable extension + 3 days follow-up)

Reference therapy: Placebo

Dose: 10 µg, 15 µg, and 20 µg

Administration: subcutaneous injection

Batch number(s): [redacted]

Criteria for evaluation:

Efficacy: Efficacy was assessed using the following criteria: the absolute change in HbA_{1c} from baseline to Week 24, the percentage of patients with HbA_{1c} <7% or ≤6.5% at Week 24, the changes in FPG and body weight from baseline to Week 24, and the percentage of patients requiring rescue therapy during the main 24-week period.

Safety: Safety was assessed by review of adverse events (AEs) and in particular treatment-emergent adverse events (TEAEs), occurrence of symptomatic hypoglycemia, clinical laboratory data, vital signs, and electrocardiogram (ECG) data.

Anti-lixisenatide antibody assessments: The status and concentration of anti-lixisenatide antibodies were determined at baseline, and at Weeks 2, 4, 24, 76, and 100; samples were also taken before the start of rescue therapy and at end of treatment, if the end of treatment visit occurred before Week 76. The samples were taken in the morning, before the injection of the investigational product.

Pharmacokinetics: Samples for assessment of plasma concentrations of lixisenatide were taken on Weeks 2, 24, 76, and 100; samples were also taken before the start of rescue therapy and at end of treatment, if the end of treatment visit occurred before Week 76. Samples were taken once prior to injection of the investigational product and then once within 1 to 4 hours postinjection. In vitro active concentration of lixisenatide was also determined (predose) at Week 24.

Statistical methods:

Efficacy: The efficacy of lixisenatide was assessed using the modified intent-to-treat population (mITT), which consisted of all patients who were randomized (analyzed "as randomized"), received at least 1 dose of double-blind investigational product, and had both a baseline assessment and at least 1 post baseline assessment of any primary or secondary efficacy variable, irrespective of compliance with the study protocol and procedures.

The primary efficacy endpoint (the absolute change in HbA_{1c} from baseline to Week 24) was analyzed using an analysis of covariance (ANCOVA) model with treatment groups (2-step lixisenatide titration and placebo arms; 1-step lixisenatide titration and placebo arms), randomization strata (screening HbA_{1c} [<8.0%, ≥8.0%], screening body mass index [BMI; <30, ≥30 kg/m²]), and country as fixed effects and using the baseline HbA_{1c} as a covariate.

A stepwise testing procedure was applied in order to ensure control of type 1 error. First, the 2-step lixisenatide titration regimen was compared with the combined placebo group. If the test was statistically significant, then the 1-step lixisenatide titration regimen was compared with the combined placebo group. Similar to the approach used for the primary endpoint, data for all continuous secondary efficacy endpoints were analyzed using the previously described ANCOVA model with the corresponding baseline value as a covariate. Data for the categorical secondary efficacy endpoints (ie, percentage of patients with HbA_{1c} <7.0% or with HbA_{1c} ≤6.5% [HbA_{1c} responders] at Week 24, and percentage of patients requiring rescue therapy during the 24-week treatment period) were analyzed using a Cochran-Mantel-Haenszel method. Results for all efficacy endpoints during the variable extension period and at the end of treatment were to be evaluated by descriptive statistics only.

Safety: The safety population was the total treated population, defined as all patients randomized and exposed to at least 1 dose of the investigational product, regardless of the amount of treatment administered. The evaluation of AEs, clinical laboratory data, vital signs, and ECG data was descriptive.

Anti-lixisenatide antibody assessments: Data concerning anti-lixisenatide antibody status and concentration were listed and summarized using descriptive statistics.

Pharmacokinetics: Individual plasma concentrations of lixisenatide and the biologically active concentration of lixisenatide were summarized using descriptive statistics.

Summary:

Efficacy results:

The superiority of lixisenatide over placebo on HbA_{1c} control was demonstrated for both the lixisenatide 2-step titration group (primary objective) and the 1-step titration group (secondary objective), based on the predefined primary analysis of the least squares (LS) mean changes from baseline to Week 24 in HbA_{1c} (LS mean change of -0.83% for the lixisenatide 2-step group, -0.92% for the lixisenatide 1-step group, and -0.42% for the combined placebo group). In comparison with placebo, the LS mean difference was -0.41% for the lixisenatide 2-step titration group ($p<0.0001$) and -0.49% for the lixisenatide 1-step titration group ($p<0.0001$). At Week 24, the percentage of responders, with HbA_{1c} ≤6.5% or <7%, was also significantly higher in each lixisenatide group versus the combined placebo group ($p = 0.0009$ for the lixisenatide 2-step titration group and $p<0.0001$ for the lixisenatide 1-step titration versus the combined placebo group for HbA_{1c} ≤6.5%, and $p = 0.0005$ for the lixisenatide 2-step titration group and $p<0.0001$ for the lixisenatide 1-step titration versus the combined placebo group for HbA_{1c} <7%). The reduction in HbA_{1c} at Week 24 was similar in antibody-positive and antibody-negative patients.

For FPG, the LS mean change from baseline to Week 24 was similar in the lixisenatide 2-step and 1-step titration groups (-0.56 mmol/L and -0.53 mmol/L, respectively) and was 0.11 mmol/L in the combined placebo group. The LS mean differences between the lixisenatide titration groups and the combined placebo group were statistically significant: LS mean difference of -0.67 mmol/L for the lixisenatide 2-step titration group, $p = 0.0004$; and LS mean difference of -0.65 mmol/L for the lixisenatide 1-step titration group, $p = 0.0007$.

For body weight, the LS mean reduction from baseline to Week 24 was similar in the lixisenatide 2-step and 1-step titration groups (-2.68 kg and -2.63 kg, respectively) and was -1.63 kg for the combined placebo group. The LS mean differences between the lixisenatide titration groups and the combined placebo group were statistically significant: LS mean difference -1.05 kg for the lixisenatide 2-step titration group, $p = 0.0025$ and -1.00 kg for the lixisenatide 1-step titration group, $p = 0.0042$.

Slightly lower percentages of patients required rescue therapy in both lixisenatide-treated groups during the main 24-week double-blind treatment period (3.1% for 2-step titration and 1.3% for 1-step titration) compared with the combined placebo group (4.4%). The percentages of patients requiring rescue therapy increased during the variable extension period. During the whole study period, the percentage of patients requiring rescue therapy was higher in the combined placebo group (38.4%) than in the lixisenatide groups (18.8% in the lixisenatide 2-step titration group and 22.8% in the lixisenatide 1-step titration group).

The clinically beneficial effects on the efficacy variables (HbA_{1c}, FPG, and body weight) observed during the main 24-week treatment period were maintained during the variable extension period.

Safety results:

The incidence of TEAEs during the whole study period was comparable across treatment groups (87.6% in the lixisenatide 2-step titration group, 85.7% in the lixisenatide 1-step titration group, and 86.3% in the combined placebo group). Five patients (1.0%) (1 patient [0.6%] in the lixisenatide 2-step titration group, 2 patients [1.2%] in the lixisenatide 1-step titration group, and 2 patients [1.3%] in the combined placebo group) had TEAEs that led to death. Overall, 59 patients had at least 1 serious TEAE, with a similar incidence rate in the lixisenatide 2-step titration group (13.0%) and the combined placebo group (13.8%), but a slightly lower incidence in the lixisenatide 1-step titration group (9.9%). In total, 19 patients (11.8%) in the lixisenatide 2-step titration group, 14 patients (8.7%) in the lixisenatide 1-step titration group, and 9 patients (5.6%) in the combined placebo group had a TEAE that led to permanent discontinuation of study treatment. The most common reason for treatment discontinuation in the lixisenatide titration groups was TEAEs from the gastrointestinal disorders system organ class, in particular, nausea (6 patients [3.7%] in each lixisenatide titration group, and none in the combined placebo group). Similar results were seen for the 24-week main treatment period.

The most commonly reported TEAE for lixisenatide-treated patients was nausea (62 patients [38.5%] with 2-step titration and 47 patients [29.2%] with 1-step titration, compared with 13 patients [8.1%] for the combined placebo group), followed by vomiting (29 patients [18.0%] with 2-step titration and 21 patients [13.0%] with 1-step titration, versus 1 patient [0.6%] for the combined placebo group). This is consistent with the known safety profile of glucagon-like peptide 1 (GLP-1) receptor agonists. However, few patients treated with lixisenatide discontinued study treatment because of nausea and/or vomiting.

Symptomatic hypoglycemia events, per protocol definition, were reported, during the whole study period for 12 patients (7.5%) in the lixisenatide 2-step titration group and 6 patients (3.7%) in the lixisenatide 1-step titration group, compared with 12 patients (7.5%) in the combined placebo group. No events of severe symptomatic hypoglycemia were reported in the study. One patient (0.6%) in the lixisenatide 2-step titration group permanently discontinued study treatment due to a TEAE of symptomatic hypoglycemia.

Injection site reactions were reported for 9 patients (5.6%) in each lixisenatide titration group and 3 patients (1.9%) in the combined placebo group; none of the reactions were serious, were considered to be severe in intensity by the Investigator, or led to permanent treatment discontinuation.

TEAEs that were adjudicated as an allergic reaction by the Allergic Reaction Assessment Committee (ARAC) were reported for 15 patients (6 patients [3.7%] in the lixisenatide 2-step titration group, 3 patients [1.9%] in the lixisenatide 1-step titration group, and 6 patients [3.8%] in the combined placebo group). Two (0.6%) of the allergic events (1 in each lixisenatide titration group) were adjudicated as possibly related to the investigational product. The ARAC diagnosis for these 2 events was anaphylactic reaction and both events led to premature discontinuation of study treatment. One of these 2 events was serious and occurred on the first day of lixisenatide treatment. No other allergic event adjudicated as an allergic reaction by the ARAC was serious or led to premature discontinuation of study treatment.

In total, 13 patients had events of changes in pancreatic enzymes, lipase, or amylase reported on the electronic case report form AE form specific for “suspected pancreatitis” during the study: 4 patients (2.5%) in each lixisenatide titration group and 5 patients (3.1%) in the combined placebo group. No confirmed case of pancreatitis was observed in the study. TEAEs of blood calcitonin increased (calcitonin levels ≥20 ng/L) were reported for 1 patient (0.6%) in each lixisenatide titration group and 1 placebo-treated patient (0.6%). Thyroid ultrasound scans and specialist evaluation showed no abnormalities in the 2 lixisenatide-treated patients. The patient in the combined placebo group was diagnosed with a left medullary thyroid cancer with lymphogen metastases.

At baseline, 7 patients (4.7%) and 4 patients (2.6%) treated with lixisenatide were already antibody-positive in the 2-step and 1-step titration groups, respectively. The percentage of patients who were antibody-positive in the lixisenatide group increased with time, to a maximum at Week 24 of 104 patients (74.3%) and 109 patients (76.2%) in the 2-step and 1-step titration groups, respectively. After 76 weeks of lixisenatide treatment, 78 patients (72.9%) and 79 patients (67.5%) in the 2-step and 1-step titration groups, respectively, were antibody-positive.

Overall, there was no substantial difference in the TEAE profile between the antibody-positive and antibody-negative population.

The vital signs data and the assessment of ECG readings did not reveal any specific safety signal. Slight decreases in systolic blood pressure, and no substantial changes in diastolic blood pressure and heart rate, were observed in both lixisenatide titration groups.

Pharmacokinetic results:

The median postinjection concentration of lixisenatide for anti-lixisenatide antibody-negative patients treated with 20 µg lixisenatide at the respective visit was 52.10 pg/mL, 76.45 pg/mL, 72.20 pg/mL, and 354.00 pg/mL at Weeks 2, 24, 76, and 100, respectively. The respective medians at predose were below the lower limit of quantification (LLOQ) at Weeks 2, 24, and 76, and was 49.20 pg/mL at Week 100.

In patients treated with 20 µg lixisenatide at the respective visit who were antibody-positive, the median postinjection concentration of lixisenatide increased with the duration of treatment: from 69.00 pg/mL at Week 2, to 438.50 pg/mL at Week 24, 571.00 pg/mL at Week 76, and 584.50 pg/mL at Week 100. The respective median at predose was below the LLOQ at Week 2 and increased to 269.00 pg/mL at Week 24, 455.00 pg/mL at Week 76, and 361.00 pg/mL at Week 100.

The biologically active concentration (predose) was above the LLOQ in 92 of 198 patients who were reported as antibody-positive at Week 24, with a median of 91.350 pg/mL. The median of the resulting active fraction (active lixisenatide/total lixisenatide) was 0.182.

Conclusions: [redacted]
Date of report: 11-Dec-2014